Clinical Efficacy and Safety of Acupuncture Rehabilitation for Post-stroke Depression: A Systematic Review and Meta-analysis

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Abstract. Objective: The most important and common psychiatric disorders after stroke include post-stroke depression, which can lead to a variety of negative health outcomes. This study was calculated to estimate the security and effectiveness of acupuncture rehabilitation in curative effects for post-stroke depression patients. Methods: As of July 2022, PubMed, Embase, Web of Science, Cochrane Library, and China National Knowledge Infrastructure were searched through electronic databases. Eligibility criteria RCTs evaluate RCTs of acupuncture rehabilitation on treatment events in depressed patients after stroke, compared to a control group. Results: Eight studies were included (n = 16,422). When combined with antidepressant/sham acupuncture efficacy, acupuncture intervention observably reduced HAMD scores (MD= -0.55,95% CI= -1.57 to -0.48, P=0.30, I^2= 0%). Meanwhile, acupuncture rehabilitation also reduced BI scores (MD= 1.87,95%CI= -3.77-7.51, P=0.51, I^2= 0%) and CGI-S score (MD=0.43,95% CI = 0.06-0.77, P =0.01, I^2 = 0%) compared with antidepressants / sham acupuncture. Second, the occurrence rate of combined negative events was dramatically lesser in the acupuncture groups, as indicated by the SERS scores (MD= -4.85,95% CI= -5.67 to -4.04, P <0.00001, I^2 = 0%) of the acupuncture groups and the antidepressant/sham acupuncture groups. Furthermore, the overall clinical outcome was observably better in the acupuncture groups (MD=1.58,95% CI =0.813.09, P =0.18, I^2 = 0%). Conclusion: Acupuncture rehabilitation intervention for post-stroke depression is safer and more effective than antidepressant/sham acupuncture.

Keywords: acupuncture; post-stroke depression; rehabilitation; meta-analysis; randomized controlled trial.

1. Introduction

The most common psychiatric disorders after cerebrovascular injury include post-stroke depression [1] which refers to a mood disorder secondary to continuous emotional depression, decreased interest, and physical fatigue after stroke [2]. And it has significantly increased the recurrence rate of neurovascular events in patients [3]. Li et al. (2018) reveal that the incidence of depression is 33% after stroke and 34% in the long term [4]. Therefore, reducing PSD is important for improving functional rehabilitation, quality of life, and prognosis of stroke patients. Until now, the exact physiopathology of PSD remains a controversial issue, but several different mechanisms of PSD have been proposed, including the monoaminergic hypothesis, HPA axis dysregulation, glutamate-mediated excitotoxicity hypothesis, neuroinflammatory response, neuronal plasticity, etc [5]. Furthermore, there is a popular belief that the occurrence of PSD is concerned with the neurotransmitters and neurotransmitter receptors [6], the dysregulation of the brain oxidant-antioxidant balance [7], and the cytokine network [8].

At present, post-stroke depression is mainly treated with antidepressants [9], but it is important to consider any potential side effects, including damage to the heart, gastrointestinal tract, sexual dysfunction, and sleep disturbances [10, 11]. The study found that patients taking medications were characterized by a low compliance rate, long reaction time, strong dependence, and large adverse reactions (e.g., headache, nausea, excitement, decreased intellective acuity, loss of memory loss, gain in weight, and metabolic disturbance [12]). Studies have indicated that antidepressants can not only destroy the nervous system, the heart, and the liver but also cause some patients to want to experience life-threatening by committing suicide [13]. In addition, antidepressants do not fully respond to a large proportion of patients [14]. From the above problems, it can be inferred that post-stroke depression is difficult to achieve complete remission by antidepressant treatment alone [9, 10].Therefore, combining pharmacological and non-pharmacological therapies is essential. Traditional Chinese acupuncture rehabilitation is an effective non-pharmacological therapy for post-stroke depression because acupuncture has very good results in regulating

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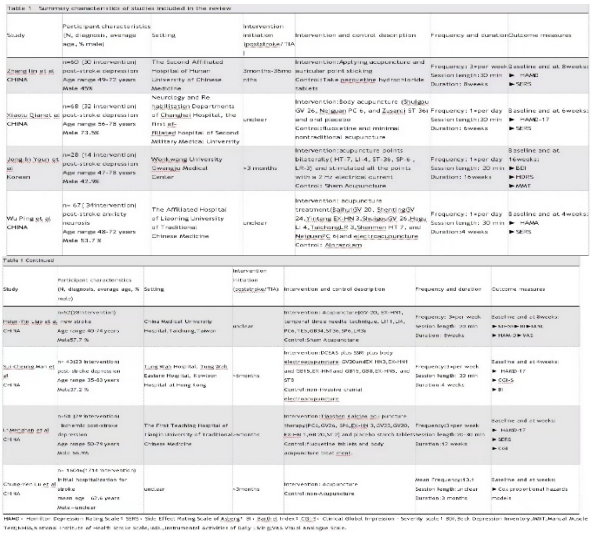
depression and improving mood and sleep [15]. Two previously published meta-analyses suggest that acupuncture rehabilitation works better compared to depressive medication [4, 16]. However, in the above studies, manual acupuncture and electro acupuncture were then separately divided into two treatments and the resulting heterogeneity makes it difficult to interpret the conclusions drawn. The newly published meta-analysis by Zhang et al. (2021) [17] was not normative and blinded to the included studies, and the findings included only the two-aspect scores, which do not adequately illustrate the conclusions drawn. Therefore, our study combined the joint intervention of the body and electric needles, incorporated into the experiment strictly by the standardized selection, demonstrating the conclusions by comparing the five aspect scores. We assessed the security and effectiveness of acupuncture rehabilitation for post-stroke depression by conducting a meta-analysis.

Table 1. Summary characteristics of studies



2. Methods

The author prepared this study in conformity with the preferred reporting project guidelines for Meta-analysis [18]. The recommendations for the systematic review manual for Operational Definition Cochrane interventions were detailed before the search began [19].

2.1 Selection criteria

We involved studies that assessed adults (age, > 18 years) with depression or anxiety disorders after stroke (ischemic or hemorrhagic) according to the WHO definitions. Randomized controlled trials evaluating the outcome of acupuncture or electro acupuncture intervention were involved only, compared with pill taking or sham intervention. Acupuncture points include body points, head points, and bilateral acupoints. Stimulating acupoints causes a sense of de qi (acidity, bloating, or numbness), and the depth of acupuncture was based on the excitement of de qi. There was acupuncture sensory transmission, which can treat mental disorders, relieve mental stress clear liver thinking, regulate climate, adjust brain function and eliminate stagnation. An intervention known as "electro acupuncture" contains a clear goal is depressive symptoms by low-frequency electrical stimulation. Only studies reporting the efficacy of CGI-S, BI, HAMD, SERS, and Efficacy, in depressed patients after stroke.

2.2 Search strategy

As of July 2022, the electronic databases search Cochrane Library, PubMed, Web of Science, and the China National Knowledge Infrastructure. Combine selected medical subject headings with free text terms involving acupuncture (e.g., acupuncture therapy, acupuncture points, moxibustion), stroke (e.g., cerebrovascular accident, cerebral infarction), to create the final search strategy of the MEDLINE. This can be used in other databases by using the appropriate Boolean operators and search symbols. At the same time, the Chinese translation is used in the Chinese databases. Scan systematic reviews for other potentially relevant studies and the reference list of all relevant studies. Our study did not involve anything in the grey document.

2.3 Study selection and data extraction

The review authors independently removed duplicated and unrelated studies from the headlines and abstracts. The whole passage of the remaining research was independently obtained and narrowly reviewed by the author. The authors independently extracted data including the study background and time frame, participants' demographic data, interventions their descriptors, and outcome measures into a pre-designed electronic spreadsheet. Collect data needed for meta-analysis, covering associated SD and the average difference between baseline and post-intervention the evaluation of outcome. Differences in data extraction or study selection were remarked on and judged by the third reviewer.

2.4 Quality assessment

The reviewers estimated the risk of error in all researches that accord with the selection standard by identifying the bias attributable to randomization, attrition bias, blinding, and reporting through the checklist. The overall high risk was for researches with a high risk of bias under different fields, while the moderate risk was for studies with ambiguous information in any domain. Low risk criteria in each domain apply to studies. Grade measures (recommendation, evaluation, progress, and assessment levels) methods were also used for assessing the quality of each outcome and measuring evidence for the tabulated data (HAMD, SERS, BI, CGI-S, post-stroke depression patient efficacy). The initial "high quality" rating of the RCT fell by one level due to serious concern (or a very serious problem on two levels), involving the risk of bias, indirect, inconsistency, or publication bias associated with associated evidence for each result.

2.5 Data analysis

The study characteristics were qualitatively integrated. The event number and total sample number were used in the meta-analysis of dichotomous variables (efficacy of post-stroke depression), and the mean difference and SD of mean difference were used in the meta-analysis of continuous variables (HAMD, SERS, BI, BI I, CGI-S). Not all research has stated numerical values of SDs before and after acupuncture. Under these circumstances, the direct contact study's authors requested missing data and, if not, we estimated the missing values by an indirect approach. We deal with heterogeneity by using a random effects model caused by the expected population (post-stroke depression, anxiety severity) and acupuncture interventions.

3. Results

Based on the search strategy of this research, 1925 articles were identified after removing duplicates; 18 full-text articles (Fig. 1) were retrieved from them. After exclusion, they were systematically reviewed and meta-analyzed in eight retained RCTs involving a total of 16,422 patients.

3.1 Quality appraisal

Relatively low risk of bias in four research, two research moderate, and two research relatively high (Fig. 2). The ratings of the quality of evidence scores for each meta-analysis result ranged from medium to very low.

3.2 Study characteristics

Eight selected randomized controlled trials engaged 16,422 eligible patients from China and Korea (Table 1). Six trials involved patients with post-stroke depression [20-25], one study involved patients with post-stroke anxiety disorders [26], and one study involved patients first hospitalized for stroke [27]. The entire regimen lasted from 4 weeks to 3 months, the duration of each treatment is 20 to 30 minutes, and the treatment is 1 to 3 times a week. Three study interventions included acupuncture and electro acupuncture [21, 24, 26], one study involved ear application [22], and three study interventions included oral placebo [22, 24, 25]. All of the experiments included in this study indicated outcome measures related to post-stroke depression, with the most frequently reported being the HAMD score (6 studies).

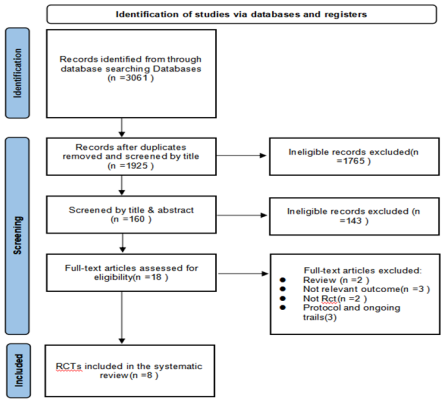


Figure 1. Flow chart for research selection process.

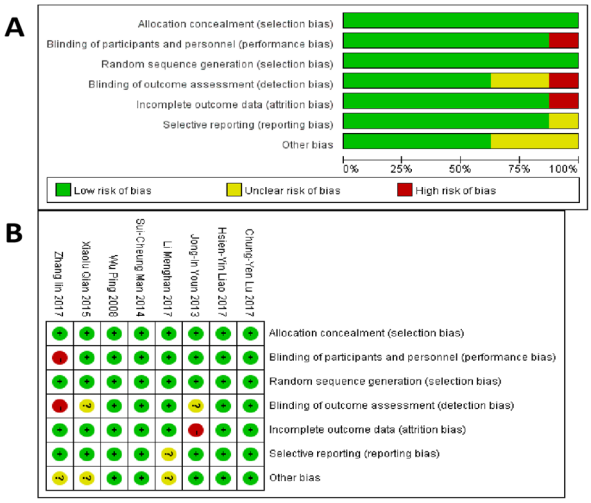


Figure 2. (A) Risk of bias: review writers' estimates of the involved researches on the percentage of items in each risk of bias;(B) Risk-of-bias summary: inspect the writers' estimates on the items expressed in each risk of bias in the involved researches

4. Quantitative synthesis (meta-analysis)

4.1 HAMD score

The HAMD data came from six studies [22-27], including 348 patients (intervention n=176), the intervention group significantly reduced the HAMD scores when compared with the sham acupuncture groups (MD= 0.00, 95%, CI= -0.99 to -0.99, and P=1.0, I^2=70%, Fig. 5A). We found that heterogeneity comes from Lin (2017) through a susceptivity analysis. Therefore, the heterogeneity was recalibrated and found to be significantly reduced (MD= -0.55, 95%, CI= -1.57 to 0.48, P=0.30, I^2 = 0%).

4.2 BI score

Acupuncture was associated with an improved BI scores (MD= 1.87, 95%, CI= -3.77 to -7.51, P=0.51, I^2 = 0%, Fig. 5B), involving two randomized controlled trials including 95 patients (n=51). Because very few studies were included [24, 27], it was impossible to find a source of heterogeneity.

4.3 SERS score

SERS data from four studies [22, 23, 25, 26], including 253 patients (intervention n=125), showed that acupuncture reduced SERS scores more significantly (MD= -0.61,95%, CI = -1.11 to -0.12, P = 0.02, I^2 = 99%, Fig. 3). We found that heterogeneity comes from Lin (2017) and Qian (2015) through a susceptivity analysis. Heterogeneity was significantly reduced when these two studies was excluded (MD=-4.85, 95%, CI= -5.67 to -4.04, P <0.00001, I^2 = 0%).

4.4 CGI-S score

Two RCTs measured the CGI-S scores, representing 101 patients (n=52), as compared to the control groups. From the summary data of these two studies, acupuncture

significantly reduced the CGI-S scores (MD = 0.43, 95%, CI = 0.06 – 0.77, P = 0.01, I^2 = 0%, Fig. 4) [24, 25].

4.5 Treatment efficacy

Three RCTs represented 195 patients (intervention n=96), in comparison with the control group. Summary data from these three experiments showed better treatment outcomes in acupuncture groups (MD = 1.58, 95%, CI = 0.813.09, P = 0.18, I^2 = 0%, Fig. 5C) [22, 23, 26].

4.6 Adverse events

Six patients out of eight RCTs had adverse events. In the acupuncture group, the most commonly recorded adverse events were causing dizziness, dry mouth, nausea, diarrhea, fainting, needle bending, needle break, hematoma, deteriorating constipation, or loss of appetite, all of which were minor adverse reactions.

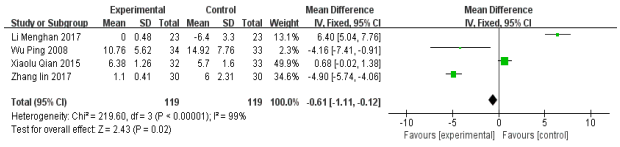


Figure 3. Forest plot of SERS scores induced by acupuncture and control intervention.

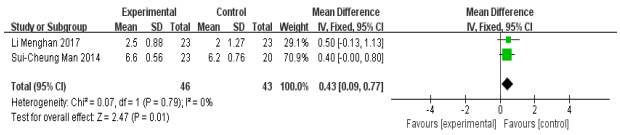


Figure 4. Forest plot of CGI-S score induced by acupuncture and control intervention

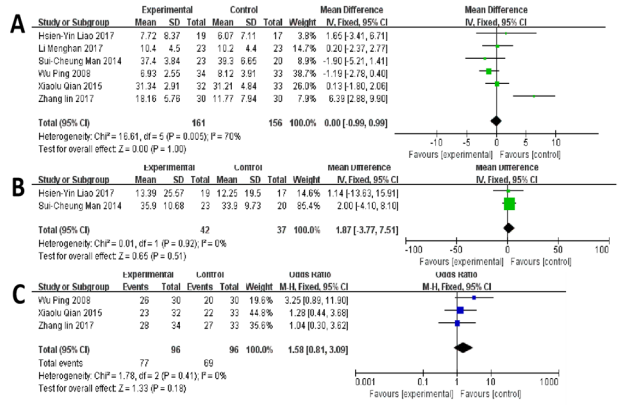


Figure 5. Forest plot of (A) HAMD scores, (B) BI scores, (C) Treatment efficacy induced by acupuncture and control intervention.

5. Discussion

The most common psychiatric disorders after cerebrovascular injury include post-stroke depression, affecting one-third of stroke patients [1]. Assessing the security and effectiveness of acupuncture rehabilitation for post-stroke depression is key to reducing the medical burden. In the studies that we included, when compared to Li (2018) [4] counted the HAMD scores, and compared with Zhang (2021) [17] counted HAMD, NIHSS, and TESS. The advantages of this study are the introduction of multiple outcome scores, including the efficacy of SERS, BI, CGI-S, and post-stroke depression patients, making the study results more comprehensive and credible. We treated studies with small heterogeneity by using fixed effects models and using sensitivity analysis. Acupuncture was more pronounced than antidepressants in reducing HAMD scores than antidepressants. These consequences are complying the preliminary consequences informed by Zhang et al. (2021) [17], But with different results from the study of Li et al. (2018) [4]. Analyzing the SERS score findings revealed that acupuncture considerably lowered the scores when compared to antidepressants, implying that acupuncture had less adverse effects. This was also validated by Li et al. [4]. From the CGI-S score, the acupuncture group had a lower overall clinical impression severity. Secondly, from the degree of patient depression, we can see that the acupuncture group is more effective than the antidepressant/sham acupuncture group. There were no important diversities between acupuncture and antidepressants in the observed improvement in Barthes, but acupuncture caused fewer adverse events. From the above scores, it is observed that the clinical treatment effect of acupuncture is very effective, which not only reduces the relevant scores, but also reduces the incidence of adverse events, which is a green and safe treatment method. By analyzing the research data, we can conclude that acupuncture rehabilitation is more useful for post-stroke depression than antidepressants, and it also relieves anxiety after stroke [26], and the treatment effect of the group with good motor function is more obvious than the group with poor motor function [21]. It is worth noting that acupuncture does not cause post-stroke depression [20]. Therefore, we conclude that acupuncture rehabilitation performs well in treating post-stroke depression, which is in line with the conclusions of other investigators [28, 29].

Acupuncture has the function of dredging meridians, regulating qi and blood, and opening the body [30]. Acupuncture rehabilitation aims to reduce functional defects and promote the overall recovery of the patient [31]. At present, there are three main ideas about the mechanism of acupuncture in the treatment of PSD. Acupuncture can affect the release of neurotrophic factors, cytokines and monoamine neurotransmitters [32]. Brain-derived neurotrophic factor (BDNF), acts as a trophic neuron when it binds to receptor tyrosine kinase (TrKB) neurons. It has been demonstrated that the lowered expression of BDNF and TrkB proteins in the cerebral cortex of patients is related to an episode of PSD. The "cytokine hypothesis of depression" points out that in some situations after PSD, inflammatory factors disrupt the balance of the body and cause metabolic abnormalities and irregular excretion of neurotransmitters. Moreover, acupuncture has been shown to increase BDNF expression in several rat experiments and acupuncture has been found to decrease the thickness of skin reaction factors in study [33]. There is still an imbalance between 5-HT and ne [37]. The effectiveness of the selective serotonin reuptake inhibitors supports that the PSD disrupts both the 5-HT and NE neurons, leading to

changes in the neuronal conduction pathways. Acupuncture can regulate the selective serotonin reuptake inhibitors and NE standards [38]. Nevertheless, the mechanism by which acupuncture treats PSD through increasing 5-HT or NE is not clear, so one of the limitations of this study includes this unknown variable. In neuroimaging studies, electro acupuncture stimulation can directly regulate the activity of brain regions related to emotional processing [34]. Thus, electro acupuncture adopts low frequency electricity and low frequency, because it can cause physiological changes in the brain more favorably, thus reducing depressive symptoms in patients [35, 36]. The experiments included in this study had no serious adverse events.

In addition, our study currently has the following limitations. First, only 1 of the eight RCTs was in Korea [21], and the rest are all Chinese, so the results of this study may not be suitable for post-stroke suppression and patients in other countries. Second, only one study had a follow-up [20], and the remaining included study experiments had a short duration and lacked a follow-up, while the other included study experiments had short durations and no follow-up. Third, in the current study, acupuncture point selection, acupuncture retention time, method of acupuncture stimulation, and electro acupuncture parameters (such as current intensity or frequency, and model of the instrument) was not limited in different studies, which may limit the reliability of our results. Finally, given that many Chinese patients have special views on acupuncture therapy, the antidepressant effects of acupuncture may come from the patients' placebo effects, which may be one of the sources of the observed heterogeneity. Acupuncture therapy is different in different theories of TCM. In general, good medical acupuncture treatments include one or both [28], so this may limit the use of all acupuncture treatments during another treatment process. Future research can be used as a research direction. Furthermore, future experiments should improve standardized reporting of acupuncture sessions, encourage acupuncture RCT to follow STRICTA guidelines, and rigorously design large-scale randomized controlled trials to fully meet the criteria for reporting interventions in acupuncture clinical trials guidelines [29].

6. Conclusion

Based on our study, the acupuncture rehabilitation intervention for post-stroke depression was safe, and the therapeutic efficacy was more pronounced than the antidepressant/sham acupuncture and reduced the incidence rate of adverse events.

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